REMARKS

Claims 1, 5, 7-9, and 11-37 are pending in the present application.

§103(a) Rejection over Shimizu in view of Sherwood

Claims 1, 5, 7-9, 11-20, 22-34, 36, and 37 are rejected under 35 U.S.C. §103(a) as being obvious over Shimizu (U.S. Patent No. 6,328,994 B1 to Shimizu et al.) in view of Sherwood (U.S. Patent No. 5,585,115 to Sherwood et al.). This rejection is respectfully traversed.

The Applicants' claimed amount of MCC is not taught or suggested. Contrary to the Examiner's understanding, Shimizu does **not** teach "the use of MCC in an amount of up to 50%" of the total weight of the tablet. Instead, Shimizu teaches 3 to 50 weight % based on only a component of the tablet; i.e., 50% "relative to 100 weight % of the orally disintegrable tablet **apart from the fine granules**" (col. 10, lines 25-29)(emphasis added). The range of MCC when based on the total weight of the tablet or composition is thus considerably less than 50%; e.g. the fine granules contain the active ingredient and are a significant amount of the total tablet.

For instance, Example 3 of Shimizu, which uses MCC, shows that 200 g of the enteric coated granules (i.e., "the fine granules") are mixed with 328.3 g of non-fine granule additives (189.7 + 30 + 60 + 15 + 2.8 + 25 = 322.5 as recited in col. 4 lines 30-40 of Shimizu). From this blend, 250 g was then tabletted (see col. 24 lines 41-45). Using these general blend proportions of about 2 parts fine granules to about 3 parts of other additives, the maximum MCC per tablet would be about 30 % (e.g. 50% of 3 parts is 1.5

parts out of a total of 5 parts or 30%). In the actual tablet of Example 3 only 60 g of MCC are used which corresponds to 11%. Other Examples have similar proportions of fine granules to additives; e.g., Example 2 uses 97.3 parts fine granules to 152.7 parts of additives or again about 2:3.

Because Shimizu's up to 50% MCC disclosure is not based on the total tablet weight but only on the weight of the additives portion, the Shimizu range of MCC is not overlapping or adjacent to the Applicants' claimed range of "at least 50%" of a silicified MCC. Thus, Shimizu does not teach or suggest the Applicants' claimed range of cellulose-based binder.

To the bridge the gap in the Shimizu disclosure, the Examiner relies on Sherwood's general teaching of the advantages of silicified microcrystalline cellulose over MCC, along with Sherwood's working Examples 10-12 in which the exemplary tablets contain 70% silicified microcrystalline cellulose. But such a combination of teachings does not teach or suggest the Applicants' claimed range of binder.

Assuming (without conceding) that MCC and silicified microcrystalline cellulose are interchangeable, the skilled worker would not have been motivated to increase the amount of silicified microcrystalline cellulose in Shimzu's hypothetically modified tablet to 70% based on Sherwood's working Examples 10-12. Increasing the amount of silicified microcrystalline cellulose in Shimzu's hypothetically modified tablet would have been expected to adversely affect the oral disintegratability of the tablet. Sherwood discloses that "[b]oth microcrystalline cellulose and silicon dioxide are substantially water insoluble" (see Sherwood at col. 9, lines 21-22). Shimizu teaches the importance of having a water soluble additive such as a sugar alcohol (e.g. mannitol) in amounts of

5% to 97%, not including the weight of the fine granules (See col. 10 lines 1-13 of Shimizu). Indeed, while the sugar may account for nearly all of the non-fine granule additives, the MCC may not. This is not too surprising given that Shimizu is making an orally disintegratable tablet. Sherwood further discloses that due to the use of silicified microcrystalline cellulose in place of MCC, "the amount of the novel excipient [silicified microcrystalline cellulose] compared to the amount of microcrystalline cellulose which must be used in a wet granulation technique to obtain an acceptable solid dosage form is **substantially reduced**" (emphasis added) (see Sherwood at col. 12, lines 9-13). Thus, according to Sherwood, replacing Shimzu's MCC with Sherwood's silicified microcrystalline cellulose would cause the skilled worker to reduce (not increase) the amount of silicified microcrystalline cellulose used.

Although Sherwood's disclosed amount of silicified microcrystalline cellulose may be bodily incorporated into Shimzu's tablet, and as the Examiner herself points out (citing *In re Keller*), "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference ... [r]ather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art" (Office Action at page 6). Here, the combined teachings of the references would have suggested that when switching to silicified microcrystalline cellulose, the skilled worker would likely use a lesser amount than the original amount of MCC used – and not a greater amount as suggested by the Examiner. The extreme[2] compacts made in Sherwood Examples 10-12 do not override the teaching

[2] Sherwood teaches that MCC binders are "typically used" in amounts of 5 to 30%. (See col. 7 lines 48-51). The 70% amount used in the comparison between MCC and silicified MCC in Examples 10-12 was clearly for demonstration purposes and not a teaching of the intended amount for making a pharmaceutical dosage form; else Sherwood's teaching that silicified MCC was a replacement for MCC would be hollow.

in Shimizu regarding the amount of MCC. That is, if the Sherwood 70% silicified MCC was attempted to be implemented into the Shimizu orally disintegrating tablet, the not greater than 50% MCC threshold would be exceeded and the amount of water soluble binder would be reduced. The Examiner has failed to explain why the worker of ordinary skill in the art would have expected such an extreme departure from Shimizu to remain a satisfactory orally disintegrating tablet. It should be noted that Sherwood does not disclose making orally disintegrating tablets, but does teach obtaining tablets of superior strength. Accordingly, there is no motivation to combine the teachings of Shimizu and Sherwood to obtain the Applicant's claimed orally disintegrating tablet containing at least 50 weight % of silicified microcrystalline cellulose.

In addition to failing to suggest the Applicants' claimed amount of silicified MCC, the applied art also fails to provide a reasonable expectation of successfully obtaining the claimed oral disintegration time of 1 to 15 seconds. That is, even if all of the above changes were made to Shimizu, there is no reasonable expectation of reducing the Shimizu tablets' exemplified disintegration time to the instantly claimed 1 to 15 seconds. Why would the worker of ordinary skill in the art have found it obvious that a tablet having a different MCC binder than Shimizu in a greater amount could dissolve faster than any of the Shimizu exemplified tablets, given the teachings in Sherwood? The Examiner has failed to identify any basis for making such a leap or for having a reasonable expectation of landing within Applicants' claimed 1-15 second orally disintegratable time. In short, it could not have been obvious that a tablet with a different binder and used in a greater amount than as taught in Shimizu would nonetheless have superior oral disintegration properties as per the instant claims.

For the reasons discussed above, claims 1, 5, 7-9, 11-20, 22-34, 36, and 37 would not have been obvious over Shimzu in view of Sherwood. Reconsideration and withdrawal of the rejection of these claims are thus respectfully requested.

§103(a) Rejection over Betzing in view of Shimizu and Sherwood

Claims 1, 5, 7-9, and 11-37 are rejected under 35 U.S.C §103(a) as being obvious over Betzing (U.S. Patent No. 5,776,492 to Betzing et al.) in view of Shimizu and Sherwood. This rejection is respectfully traversed.

One of ordinary skill in the art would not have been motivated to modify the teachings of Betzing based on Sherwood (or Shimzu) to replace Betzing's MCC with Sherwood's silicified microcrystalline cellulose to obtain the claimed tablet, nor would the skilled worker have had a reasonable expectation of success in doing so.

As previously argued, a worker of ordinary skill in the art would expect from Betzing that the precise excipients in the specific ratios as disclosed throughout Betzing (e.g., col. 2, line 58 to col. 3, line 28) must be used, and that replacing Betzing's MCC with Sherwood's silicified microcrystalline cellulose would at best yield uncertain results and more likely would further slow the disintegration rate.

Specifically, at column 3, lines 20-28, Betzing indicates that replacing MCC with either water soluble lactose or water insoluble calcium hydrogen phosphate results in a significant decrease in the disintegration rate (see also comparative Examples 6 and 7). That a water soluble sugar produces a slower disintegration rate is counter-intuitive. That a water insoluble excipient such as calcium hydrogen phosphate also decreased the

disintegration rate counsels against the use of silicified microcrystalline cellulose – which contains the water insoluble excipient silicon dioxide. Moreover, Betzing indicates that a certain amount of starch is useful in stabilizing disintegration times over a variety of tablet hardness (see col. 3, lines 7-19), but that too much starch/not enough MCC can actually decrease disintegration rates (col. 3, lines 22-25). Thus, one skilled in the art would have expected such a modification to at best yield unpredictable results, and likely an undesirable decrease in disintegration rate.

The Examiner fails to address the deficiency in Sherwood, namely that Sherwood fails to teach or suggest the suitability of using silicified MCC in forming an orally disintegrating tablet. Note that "disintegration" is not tantamount to oral disintegration as used in Shimizu or the present application. Most immediate release tablets contain a "disintegrant," yet most tablets do not dissolve in the patient's mouth in less than 15 seconds.

Because replacing Betzing's MCC with Sherwood's silicified microcrystalline cellulose would have unpredictable results, and likely an undesirable decrease in disintegration rate, one of ordinary skill in the art would not have found the present invention, which requires faster oral disintegration rates, to have been obvious. Accordingly, claims 1, 5, 7-9, and 11-37 would not have been obvious over Betzing in combination with Shimzu and Sherwood.

Conclusion

All claims pending in the present application define novel, patentable subject matter. Reconsideration of the rejection and allowance of the application are requested.

Should the Examiner have any questions regarding this application, she is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,

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